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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/820,843	04/09/2004	Bernard Dujon	3495.0111-14	9487

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EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 10/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/820,843	DUJON ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 1946*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04/09/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 04/06/06 has been acknowledged.

Claims 1-22 are canceled.
Claims 23-39 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 23-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for introducing at least one site directed double strand break in DNA of an isolated cell, does not reasonably provide enablement for a method of enabling for a method for introducing a site directed double strand break in DNA of a cell in-vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of Invention

The invention relates to a method for inducing a site directed double strand break in DNA of an organism.

Breadth of Claims and Guidance Provided in the Specification

The scope of invention as claimed encompasses a method inducing site directed double strand break in DNA of a cell in-vivo. At best the specification teaches insertion of I-Sce-I site via homologous recombination in isolated mouse NIH3T3 fibroblast and mouse PCC7-s multipotent cell lines using viral vectors (page 64-67, table-1, page 84.

Furthermore, the specification teaches genetic recombination, especially the homologous recombination in the making of transgenic yeast (page 3, para.1-2, example 1, 2 and 3). The specification further proposes that in gene therapy, cells from a patient can be infected with a I-Sce I site containing retrovirus, screened for integration of the defective retrovirus and then co-transformed with the I-Sce I endonuclease producing vector and the donor sequence. The specification further proposes that appropriate cells include hepatocytes, skin cells, endothelial cells stem cells, hematopoeitic tissue, of blood vessels or any stem cells (spec pages 87-88). However the specification as filed fails to disclose a single working example, which establishes the genetic manipulation of any cell (as claimed) in any animal (in-vivo) via method of gene therapy.

State Of Art And Predictability

The art at the time of filing teaches that the method associated with gene delivery/ therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. For example, it has been difficult to predict the efficiency and out come of transduced genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors. Although the retroviral vectors are the vectors of choice, they require target cells to be in cycling state for the successful delivery of gene of interest. On the other hand vector comprising DNA viruses and liposome coated DNA have been used to transduce non dividing cells but this results in a transient expression due to non-integration of transgenes in host cells. Furthermore, in vitro gene transfer studies are not predictive of in vivo gene therapy because gene transfer frequency is much higher in-vitro models where most of cells are under going rapid cell division, which is quite not the case in-vivo environment. In addition, besides the limitations in gene transfer the problem to selectively target cells in vivo is still one of the most difficult obstacles to overcome. The viral particles binds to many cells they encounter in vivo and therefor would be diluted

out before reaching their targets. For example, considering the scope of invention as claimed the specification fails to disclose any method that would enable one skilled in the art to genetically modify a stem cell progenitor (or progeny thereof) circulating in the blood of an animal (in-vivo) without undue amount of experimentation. (see Goncalves, BIOESSAYS. 27(5):506-517, 2005; Juengst, BMJ, 326:1410-11, 2003, Rosenberg et al, SCIENCE 287:1751, 2000). In instant case the invention as claimed requires repeated genetic modification of single target cell in vivo. The first step involves the insertion of I-SceI sites in target cells followed by delivery of a genetic construct encoding the I-SceI endonuclease and a genetic sequence of interest. The specification fails to provide any evidence that such an approach is predictable in targeting any cell in-vivo.

On the other hand the scope of invention as claimed encompasses genetically modified organism that encompasses a transgenic organism. The scope of invention as claimed encompasses a cell present in a transgenic organism comprising at least one I-SceI site. The state of transgenic art at the time of filing was such that phenotype of an animal is determined by a complex interaction of genetics and environment. (Wood. COMP. MED. 50(1): 12-15, 2000, see page12). The transgene expression and physiological consequences of transgene products in non-mouse mammals are not always accurately predicted among various species of mammals. Furthermore, the lack of understanding of essential genetic control elements make it difficult to predict the behavior of a transgene in any and all animals because the expression is influenced by position effect in transgenic animals. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct and the site of integration, are the important factors that govern the expression of a transgene. The cis acting elements of one species may interact with different transactivating factors in other species. Many biochemical pathways are plastic in nature, which reflects the ability of the embryo to use alternative gene when the preferred gene is modified. It is known in the art that the level and the specificity of a transgene as well as the phenotype of the transgenic animal are greatly dependent upon the specific expression vector used (Kappel et al. CURRENT OPINION IN BIOTECHNOLOGY 3:558-553 1992). In addition microinjection is a low efficiency process and there are numerous

parameters that influence the efficacy or producing transgenic animals by pronuclear microinjection. The state of the transgenic art concludes that poor embryo survival, low transgene integration rate and unpredictable transgene behavior are the three primary contributors to pronuclear microinjection inefficiencies.

The disclosure "shall inform how to use, not how to find out how to use for themselves." See In re Gardner 475 F.2d 1389, 177 USPQ 396 (CCPA 1973). At issue, under the enablement requirement of 35 U.S.C. 1 12, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). In instant case considering the scope of invention, it would require an extensive and undue amount of experimentation to practice the invention as claimed especially in context genetic modification in-vivo or development of a transgenic animal. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed. Claims drawn to an isolated host cell would obviate the instant rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 recites claim limitation "providing the Group I intron endonuclease to said cell". It is unclear how the endonuclease is provided to the cell in this context.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 23-39 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 6,610,545 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of invention as claimed is drawn to a method of introducing at least one site directed double strand break in DNA of a cell having at least one Group I intron encoded endonuclease site by providing a Group I intron encoded endonuclease which is encompassed by the subject matter claimed in the US 6,610,545 B2. Therefore the method as claimed in the instant application is prima facie obvious in view of US 6,610,545 B2 which claims a method for site directed

genetic recombination in an organism having at least one HO endonuclease recognition site (i.e. I-SceI) by providing an expression vector that express HO endonuclease (i.e. I-SceI endonuclease) which results in cleaving of nucleic acid sequences containing HO endonuclease site(s) i.e. I-SceI, thus resulting in a double stranded break in the nucleic acid sequence of the cell. Therefore the invention of instant application is prima facie obvious in view of invention as claimed in US 6,610,545 B2.

Claim 23-39 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6,238,924 B1 (ref. of record).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of invention as claimed is drawn to a method of introducing at least one site directed double strand break in DNA of a cell having at least one Group I intron encoded endonuclease site by expressing a Group I intron encoded endonuclease which is encompassed by the subject matter claimed in the US 6,238,924 B1. Therefore the method as claimed in the instant application is prima facie obvious in view of US 6,238,924 B1 which claims a method for site directed genetic recombination in an organism having at least one I-SceI sites by providing an expression vector that express I-SceI endonuclease which results in cleaving of nucleic acid sequences containing I-SceI site(s), thus resulting in a double stranded break in the nucleic acid sequence of a cell in an organism. Therefore the invention of instant application is prima facie obvious in view of invention as claimed in US 6,238,924 B1.

Claim 23-39 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 27-29 of U.S. Patent No. 5,962,327 (ref. of record). Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of invention as claimed is drawn to a method of introducing at least one site directed double strand break in DNA of a cell having at least one Group I intron encoded endonuclease site by providing a Group I intron encoded endonuclease which is encompassed by the subject matter as claimed in the US 5,962,327. Therefore the method as claimed in the instant application is prima facie obvious in view of US 5,962,327 which claims a method for site directed

genetic recombination in an organism having at least one I-SceI sites and by providing an expression vector that express I-SceI endonuclease which results in cleaving of nucleic acid sequences containing I-SceI site(s), thus resulting in a double stranded break of nucleic acid sequence in the cell. Therefore the invention of instant application is prima facie obvious in view of invention as claimed in US 5,962,327.

Claim 23-39 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 5,792,632. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of invention as claimed is drawn to a method of introducing at least one site directed double strand break in DNA of a cell having at least one Group I intron encoded endonuclease site by providing a Group I intron encoded endonuclease which is encompassed by the subject matter claimed in the US 5,792,632. Therefore the method as claimed in the instant application is prima facie obvious in view of US 5,792,632, which claims a method for inducing homologous recombination in a cell having at least one I-SceI sites by providing an expression vector that express I-SceI endonuclease which results in cleaving of nucleic acid sequences containing I-SceI site(s), thus resulting in the deletion of nucleic acid sequence in the cell. Therefore the invention of instant application is prima facie obvious in view of invention as claimed in US 5,792,632.

Claims 23-39 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 31-50 of copending Application No. 10/152,994 (US 20030182670, 2003). Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of invention as claimed is drawn to a method of introducing at least one site directed double strand break in DNA of a cell having at least one Group I intron encoded endonuclease site and by providing a Group I intron encoded endonuclease which is encompassed by the subject matter claimed in the App. No. 10/152,994. Therefore the method as claimed in the instant application is prima facie obvious in view of App. No. 10/152,994, which also claims a method of deleting a target nucleic acid sequence in cell having two I-SceI restriction site and by transfecting the cells with a

plasmid encoding the I-SceI endonuclease. Therefore the invention of instant application is prima facie obvious in view of invention as claimed in 10/152,994. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 23-39 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 24-40 of copending Application No. 10/931,246 (US 20050032223, 2005). Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of invention as claimed is drawn to a method of introducing at least one site directed double strand break in DNA of an organism having at least one Group I intron encoded endonuclease site and by providing a Group I intron encoded endonuclease which is encompassed by the subject matter claimed in the App. No. 10/931,246. Therefore the method as claimed in the instant application is prima facie obvious in view of App. No. 10/931,246, which also claims a method for introducing a double-stranded break into a plant or animal cell having Group I intron encoded endonuclease recognition site by providing to the cell an expression vector or protein encoding Group I intron encoded endonuclease.

Therefore the invention of instant application is prima facie obvious in view of invention as claimed in 10/152,994. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**

SUMESH KAUSHAL
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